FERRING
PHARMACEUTICALS

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Appeal Against FAD - Degarelix for treating advanced hormone-dependent prostate cancer

Ferring wishes to appeal the Final Appraisal Determination ("FAD") for degarelix in advanced hormone-dependent prostate cancer on the grounds set out below. In summary, Ferring challenges the more restrictive recommendation in the FAD compared with the ACD on the basis that the change should have resulted in additional consultation (through the issue of a second ACD) and also because it lacks transparency and there are no adequate reasons for the change. We also consider that the failure to make a positive recommendation for the sub-group of patients at-risk of cardiovascular disease is unreasonable and exceeds NICE powers. Finally, a recommendation for an acute sub-group of patients such as those at risk of spinal compression must be accompanied by clear guidance on initiation and maintenance of dose to render the guidance sufficiently clear to the NHS. A failure to include such guidance is unfair and an abuse of power.

Ferring wishes to be heard at an oral hearing on all of the grounds below. However, Ferring is content for Ground 1.2(b) to be handled by written submissions as it recognizes that fundamental right arguments, including fundamental human rights, are a complex area of law. We appreciate that NICE has considered certain human right arguments in the past, but a case-by-case assessment is required in each case. In any event, this ground is broader than human rights and covers the Charter of Fundamental Rights, which has the force of EU law following the Lisbon Treaty. Moreover, where there is a potential infringement of human rights -- as is the case if patients are exposed needlessly to cardiac events and potential death -- then more is required of NICE by way of justification before the Appeal Panel can accept that the FAD is reasonable rather than unreasonable.[1]

Grounds of Appeal

Ground 1 (a) – NICE has failed to act fairly

Ground 1.1(a) NICE failed to issue a second ACD following a substantial change to the preliminary recommendations that significantly reduces the number of eligible patients that can be treated with degarelix.

The recommendation in the ACD is as follows:

Degarelix is recommended as an option for treating advanced hormone-dependent prostate cancer, only in people with spinal metastases ***who are at risk of impending*** *spinal cord compression.*
(Emphasis added)

[1] *R v Ministry of Defence, ex p. Smith* [1996] QB 517, 554 per Sir Thomas Bingham MR

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However, this recommendation was changed in the FAD to state:

> *Degarelix is recommended as an option for treating advanced hormone-dependent prostate cancer, only in adults with spinal metastases* ***who present with signs or symptoms of*** *spinal cord compression.* (Emphasis added).

This is a much more restrictive recommendation as it excludes patients who are at-risk of spinal cord compression and limits it to those who actually have signs or symptoms of spinal cord compression. Our view and the view of clinical experts is that this recommendation significantly reduces the number of eligible patients from approximately 3,520 patients per year to less than 520 patients, which is a 85.2% drop (minimum), and could be more as clinical practise is geared towards preventing MSCC from happening.

According to NICE's own procedures, substantial revisions of the ACD that involve a major change in the recommendations should result in a second ACD being issued or at the very least consideration of issuing a second ACD (paragraph 3.5.35 of the Guide to the Single Technology Appraisal Process, 2010 ("STA Guide")).[2] Issuing a second ACD would have resulted in a fairer process in that NICE would have been able to explain the reason for its more restrictive recommendation, and allow consultees such as Ferring to comment on the change. Depriving Ferring (and others) of this opportunity is unfair.

Please note that Ferring took steps to address this unfairness at the earliest opportunity by writing to Professor Longson on 14 April 2014 setting out its concern. However, NICE responded to Ferring explaining that the only way to address this point was to appeal the FAD.

Ground 1.2(a) The decision in the FAD to restrict use of degarelix to patients with spinal metastases who have actual spinal compression (as opposed to those who are "at risk" of spinal compression) lacks transparency and fails to give adequate reasons

The decision to restrict the recommendation so that only patients with signs or symptoms of spinal compression are eligible lacks transparency and is therefore unfair as a matter of law as well as NICE's own published guidelines (see paragraph 3.5.4 of the STA Guide). Nowhere in the FAD or in accompanying documents is there a clear explanation for this restrictive change. Moreover, no consultee or commentator argued or requested that the recommendation in the ACD be narrowed or the wording changed.

In the ACD, the rationale for recommending degarelix for at risk patients is set out in the following key paragraphs:

3.33 The ERG undertook exploratory analyses for patients with spinal metastases with actual or impending spinal cord compression, because expert opinion suggested that this subgroup could potentially benefit more from treatment with degarelix. Because of lack of data to conduct this

[2] *See http://www.nice.org.uk/media/42D/B3/STAGuideLrFinal.pdf*

exploratory analysis, the ERG ***assumed that patients receiving degarelix would not have spinal cord compression*** *and that the efficacy of degarelix and LHRH agonists in terms of PSA progression and overall survival was equivalent. The ERG stated that because the rate of spinal cord compression in this subgroup was unknown, it presented the results for rates of 5%, 10% and 50%. The ERG noted that based on the assumption of equivalent efficacy in terms of PSA progression and overall survival between degarelix and LHRH agonists, the QALY gain for degarelix was higher compared with triptorelin because of the lower utility decrement associated with spinal cord compression. The ERG concluded that if the rate of spinal cord compression in this subgroup was higher than 3.5%, degarelix would be dominant compared with triptorelin (that is, less costly and more effective).* (Emphasis added).

The Appraisal Committee concluded:

4.11 The Committee heard from the clinical specialists and patient experts that degarelix was particularly beneficial for people with spinal metastases ***who are at risk of impending spinal cord compression.*** *It also heard from the clinical specialists that not all patients with metastases are at risk of having spinal cord compression and the proportion of patients at risk is small. The Committee acknowledged that although the proportion of patients at risk could be small, spinal cord compression is a serious and complex adverse event. The Committee noted that the manufacturer did not present any data on spinal cord compression because it did not occur in the included trials. The Committee acknowledged that there was a known relationship between testosterone suppression, no risk of surge and flare and prevention of spinal cord compression. Therefore, it concluded that degarelix may offer potential benefit for people with spinal metastases* ***who are at risk of*** *impending spinal cord compression compared with LHRH agonists. (Emphasis added).*

[…]

4.19 The Committee was persuaded, based on the ERG's analyses, that if the rate of spinal cord compression in this subgroup was higher than 3.5% degarelix could be dominant (that is, less costly and more effective) compared with triptorelin. If the rate of spinal cord compression was lower than 3.5% degarelix could still be cost effective compared with triptorelin. On balance, the Committee concluded that based on comments from the clinical specialists and patient experts, who noted that degarelix provided an important benefit for people with spinal metastases ***who are at risk of impending spinal cord compression*** *for which there are no treatments available, and the ERG's exploratory analysis, degarelix was a cost-effective use of NHS resources and could be recommended as an option for treating advanced hormone-dependent prostate cancer only for people with spinal metastases* ***who are at risk of*** *impending spinal cord compression.*

The ACD is clear, therefore, that clinical specialists and patient experts had confirmed that degarelix provides an important benefit for patients at risk of impending spinal cord progression.

The publicly available comments on the ACD do not contain any reference to the phrase "*signs or symptoms of spinal cord compression*". In addition, there does not appear to be any consultee or commentator arguing that the recommendation should be narrowed or the wording changed. However, some of the patient groups appear to have interpreted the recommendation more narrowly:

> *"I believe the patients will be disappointed that the committee have only recommended the use of this drug when a patient has impending spinal compression from metastatic disease." (Prostate Cancer Support Federation)*
>
> *"Prostate Cancer UK was pleased to learn that NICE are proposing to recommend the use of degarelix as an option for hormone-dependent prostate cancer, only in people with spinal metastases who are at risk of impending spinal cord compression."*

To this, the Appraisal Committee responded:

> *"Comment noted. The final draft guidance recommends degarelix as an option for treating advanced hormone-dependent prostate cancer, only in people with spinal metastases who present with signs or symptoms of impending spinal cord compression (please see section 1.1 of the FAD)."*

The Appraisal Committee's language in its response was adopted in the final recommendation. The "at risk" wording in the body of the ACD (see key paragraphs above) was also changed to suggest that clinical specialists and patient groups had referred to degarelix providing an important benefit for people with spinal metastases "*who present with signs or symptoms of spinal cord compression*" (paragraph 4.22 of the FAD). Yet as far as we are aware no clinician or patient group made any such statement or submission.

Moreover, NICE relies on the ERG's exploratory analysis of spinal cord progression in making the recommendation in both the ACD and the FAD. It is not clear, therefore, why the same exploratory analysis provides two different recommendations -- one for at risk patients (the ACD) and the other for those with actual signs or symptoms of spinal compression (the FAD). This lack of transparency is compounded by the fact that the basis of the ERG's exploratory analysis is not available to Ferring or other commentators and so it is not possible for Ferring to check or comment meaningfully on the analysis. A simple reading of paragraph 4.22 of the FAD suggests that the ERG's exploratory analysis included at risk patients, *i.e.*, patients at risk of impending or actual spinal compression. This is because "*it was assumed that people receiving degarelix would not have spinal cord compression*". But it is impossible to know this for sure or to understand the basis for the conclusion.

Had a second ACD been issued, Ferring would have had the opportunity to highlight these points. In the absence of a justifiable, open and transparent reason for the change and an opportunity for Ferring and others to comment on it, then the original wording of the ACD must be maintained.

Ground 1.3(a) The FAD recommendation is not sufficiently clear, precise of understandable for the NHS and is therefore not in accordance with the STA Guide or principles of good administration.

The recommendation in the FAD is for a sub-group of patients. The sub-group at issue (at-risk of impending or actual spinal compression) is a very acute set of patients who essentially are in need of emergency care. When recommendations are being made in the sub-group context, we consider that it is vital to emphasise the need to adhere to the dosing and administration requirements set out in the product licence relating to initiation and maintenance. A failure to make this specific point means that the recommendation is not sufficiently clear or precise.

For example, there is a risk (a view shared by clinical experts) that clinicians would consider that the product is recommended only when a patient is suffering spinal compression and that such patients would receive an initial dose of degarelix in the hospital setting and then once that person is back in the community, the treatment could be switched to a comparator treatment option (e.g., LHRH agonist) and so the patient would not receive the maintenance dose as required under the product licence. There is no evidence for switching after an initiation dose and no long-term data exists to demonstrate whether this approach for this specific sub-group would have a negative impact on patients. We appreciate that physicians should ordinarily be able to review the product licence for themselves, but this is not always possible in a hospital setting and so it would be clearer for prescribers if the following statement was added to the recommendation:

> *Once initiated, treatment should be maintained until the initiating NHS clinician considers it appropriate to stop.*

Not only is this consistent with the degarelix licence, but it is also consistent with the assumptions upon which the ERG, and hence the Institute, based its analysis (see para. 3.33 of the FAD).

Ground 1 (b) – NICE has exceeded its powers

Ground 1.1 (b) The failure to recommend the use of degarelix in patients at-risk of suffering cardiovascular events is in breach of the NICE Charter.

Ferring submitted evidence that showed a 56% overall reduction in the risk of cardiac events in men with pre-existing cardiovascular disease who associated with the use of degarelix (Albertsen *et al* (2013)). The Appraisal Committee rejected this evidence largely on the basis that it was hypothesis-generating. Yet the size of the reduction is unprecedented and this effect appears to have been lost on the Committee.

Ferring also submitted a pooled analysis and meta-regression analysis to assess the risk of cardiovascular events. The ERG criticized these analyses, in particular by saying that the meta-regression analysis produced more favourable *p*-values than the individual trials. But this reasoning is flawed as the whole point of conducting a meta-analysis is to produce more favourable p-values. In any event, the Hazard ratios from the individual studies are all consistent with the overall finding in the Albertsen paper.

In addition to Ferring's submissions, a number of clinical specialists also submitted independent expert opinion on the potential reduction in cardiovascular risk. For example, the following comments on the ACD was made by an NHS cardiologist through the NICE website:

> *Degarelix has fewer CVS risks than LHRH agonists, and my calculations suggest that the NICE recommendation in effect to continue using LHRH agonists rather than degarelix* ***will result in some 3,500 excess CVS events per year in the UK, including heart attack and death****….There have been multiple trials raising concerns over LHRH agonists, so much so that 4 eminent American medical societies (including the American Heart Association and American Cancer Society) in 2010 issued a scientific advisory greatly raising concerns about the cardiovascular risk factor side effect profile of LHRH agonists. These were most likely in those with pre-existing cardiovascular disease (about 1/3 of prostate cancer patients). This is worrying and requires serious thought and study for prevention.* ***The cardiovascular data on degarelix versus LHRH agonist is sufficiently compelling to believe, and adopt as the default position. If NICE do not do so, the likelihood is that patients will die needlessly.*** (Emphasis added).

The Appraisal Committee rejected these submissions despite the clear view of cardiologists and oncologists (as well as Ferring) that the data on cardiovascular risk provide "*consistently strong signals*" to warrant a positive recommendation for this sub-group of patients. As the comments above make clear, the failure by NICE to make such a recommendation exposes patients to needless death and suffering from cardiac events.

Aside from the clear ethical and human right issues that this poses for treating physicians and patients (see below), it is in breach of the NICE Charter, which requires NICE to produce guidance and recommendations that seek to prevent and treat illness (paragraph 1, NICE Charter April 2013 adopted pursuant to Regulation 14 of The National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013). Rather than making a recommendation that seeks to prevent and treat ill health, the recommendation (or non-recommendation) in fact restricts patients and physicians to a treatment option that has a much worse cardiovascular profile despite the evidence for degarelix that on balance and with clear support from cardiologists points to a benefit for this sub-group.

Ground 1.2 (b) The failure to recommend the use of degarelix in patients at-risk of suffering cardiovascular events is in breach of fundamental rights.

For the reasons stated under Ground 1.1(b), the failure to make a recommendation in the sub-group of patients at-risk of cardiovascular disease exposes such patients to needless risk of heart attack and death. A number of fundamental rights are potentially engaged under the European Convention on Human Rights ("Convention") and the Charter of Fundamental Rights of the EU ("Charter"), including the following:

- Art. 2 of the Convention and Art. 2 of the Charter governing the right to life;
- Article 3 of the Convention and Art. 4 of the Charter governing inhuman or degrading treatment;
- Art. 3 of the Charter governing respect for a person's physical and mental integrity;
- Article 8 of the Convention and 7 of the Charter governing the right to family life and privacy;
- Article 14 of the Convention and Art. 21 of the Charter that prohibits discrimination

Ground 1.3(b) The failure to provide a clear recommendation for a specific sub-group by omitting important initiation and maintenance information is in breach of the NICE Charter

For the reasons set out under Ground 1.3(a), the failure by NICE to balance a recommendation for an acute set of patients by emphasising the need to ensure that an initiation and subsequent maintenance doses are provided to these patients means that NICE has failed to make a clear case for the adoption of this technology to the NHS as required under paragraph 4 of the NICE Charter. The recommendation will lead to confusion that will have an impact on the adoption of this NICE guidance.

Ground 2 – The recommendation is unreasonable in light of the evidence submitted to NICE

Ground 2.1 The assumptions upon which the ERG and Appraisal Committee has based their assessment are unreasonable in light of the evidence of cardiovascular risk submitted.

As indicated by section 4.19 of the FAD, the Institute's assessment of the cost-effectiveness of degarelix was based on the following assumptions (see FAD para 3.33):

- "treatment with degarelix and LHRH agonists would continue until death, in line with clinical practice and their licensed indications
- no differential treatment effect of degarelix compared with LHRH agonists in terms of PSA progression or death
- the proportion of patients receiving chemotherapy after PSA progression would be 70% and the proportion of patients receiving abiraterone would be 70%
- the same rate of fractures for people receiving degarelix and LHRH agonists
- the same rate of cardiovascular events for people receiving degarelix and LHRH agonists."

While Ferring disagrees with a number of these assumptions because it fails to reflect the mechanisms of action of the relevant products, the company considers that the final assumption that the rate of cardiovascular events is the same for patients receiving degarelix and LHRH agonists is the same is unreasonable given the evidence submitted to NICE by Ferring and clinical experts.

Ground 2.2 The failure to recommend degarelix for patients at risk of cardiovascular disease is unreasonable in light of the evidence submitted

For the reasons stated in section 1.1(b) above, the decision not to recommend degarelix for the sub-group of patients at risk of cardiovascular events is unreasonable given the evidence submitted to NICE by Ferring and clinical experts.

Based on the above, we would like to request that our appeal is heard at a public meeting of the Institute's Appeals Panel. I look forward to hearing your response to our points in due course.

Yours faithfully

[redacted]

General Manager
Ferring UK